Efficacy and Safety of Inhaled Insulin (Exubera) Compared With Subcutaneous Insulin Therapy in Patients With Type 1 Diabetes

Results of a 6-month, randomized, comparative trial

Teresa Quattrin, md[1]
André Bélanger, md[2]
Nancy J.V. Bohannon, md[3]

Sherwyn L. Schwartz, md[4]
for the Exubera Phase III Study Group

OBJECTIVE — The aim of this study was to determine whether premeal pulmonary delivery of rapid-acting, dry-powder insulin (Exubera) plus Ultralente could provide glycemic control comparable to a conventional insulin regimen in type 1 diabetes.

RESEARCH DESIGN AND METHODS — Three hundred thirty-five subjects were randomly assigned to receive either premeal inhaled insulin plus bedtime Ultralente or two to three injections of regular and NPH insulin for 24 weeks. The primary end point was a change in HbA_{1c}.

RESULTS — Mean decreases in HbA_{1c} values were comparable for inhaled (8.1–7.9%) and conventional groups (8.1–7.7%) (adjusted treatment group difference 0.16% [95% CI −0.01 to 0.32]). There were greater reductions for inhaled versus conventional regimen in fasting and postprandial plasma glucose (adjusted mean change differences −25.17 and −30.28 mg/dl, respectively [95% CI −43.39 to −6.95 and −54.58 to −5.97, respectively]). Hypoglycemia (events/subject month) was lower for the inhaled (8.6) versus the conventional (9.0) group (risk ratio, 0.96 [95% CI 0.93–0.99]). In subjects receiving inhaled insulin, increased insulin antibody levels were observed, but there were no associated clinical or laboratory changes. Adverse events were comparable between groups. Mild to moderate cough was more frequent in the inhaled insulin group (27 vs. 5%) but decreased during the treatment. Pulmonary function tests were not different between the groups except for a greater decrease in carbon monoxide diffusing capacity in the inhaled insulin group. Treatment satisfaction was greater in the inhaled than in the conventional group.

CONCLUSIONS — Inhaled insulin is effective, well tolerated, and well accepted in patients with type 1 diabetes and provides glycemic control comparable to that with a conventional insulin regimen.

Diabetes Care 27:2622–2627, 2004

● ●

The long-term benefits of tight metabolic control in prevention and reduction of microvascular complications of type 1 diabetes are well established (1,2). In type 1 diabetes, lack of acceptance of continuous subcutaneous insulin delivery or multiple daily injections represents barriers to the achievement of optimal HbA_{1c} values.

Pulmonary insulin delivery represents an alternative route of insulin administration (3,4), eliminating the need for preprandial injections. Inhaled insulin is absorbed more rapidly and is cleared at a faster rate than human regular insulin injected subcutaneously (4). A novel dry-powder insulin formulation and aerosol delivery device have recently been developed. Pharmacodynamic data from a randomized, open-label, comparative, single-dose study using this system showed that the onset of action of inhaled insulin is similar to that observed with insulin lispro, whereas duration of action is slightly longer (5). A small phase two study has also demonstrated that inhaled insulin given 10 min before mealtimes, combined with a long-acting insulin injection at bedtime, is an effective and well-tolerated alternative to preprandial subcutaneous insulin injections in type 1 diabetes (6). Moreover, a potential for improved compliance exists because inhaled insulin is better accepted by patients compared with subcutaneous injections (6,7).

This study enrolled patients with type 1 diabetes who were not pursuing intensive diabetes management and was aimed to determine whether pulmonary delivery of rapid-acting insulin (Exubera) plus a single subcutaneous injection of Ultralente could provide glycemic control comparable to a conventional subcutaneous insulin regimen (9) and to examine the safety, tolerability, satisfaction, and quality of life of the inhaled insulin regi-

men compared with the conventional insulin regimen.

RESEARCH DESIGN AND
METHODS

Male and female patients ($n = 416$) with type 1 diabetes were screened at 41 centers across the U.S. and Canada. Inclusion criteria were as follows: *1*) diabetes duration for 1 year or more; *2*) age 12–65 years; *3*) a regimen of two or more injections of insulin (or insulin analog) per day for at least the previous 2 months; *4*) HbA$_{1c}$ 6–11%, fasting plasma C-peptide ≥ 0.2 pmol/ml, and BMI ≤ 30 kg/m^2; *5*) compliance with self-monitored blood glucose measurement; and *6*) signed informed consent. Exclusion criteria were as follows: *1*) poorly controlled asthma or clinically significant chronic obstructive pulmonary disease, or other significant respiratory disease; *2*) smoking during the previous 6 months; *3*) significant abnormalities on a screening chest X-ray; *4*) abnormal pulmonary function at screening including carbon monoxide diffusing capacity (DL$_{CO}$) <75%, total lung capacity (TLC) <80% or >120%, forced expiratory volume in 1 s (FEV$_1$) <70% of predicted; *5*) clinically significant major organ system disease with the exclusion of diabetes microvascular complications; *6*) abnormal electrocardiogram; *7*) abnormalities on laboratory screening; *8*) therapy with systemic glucocorticoids; *9*) drug or alcohol dependence; *10*) history of two or more severe episodes of hypoglycemia within the previous 6 months; *11*) any hospitalization or emergency room visit because of poor diabetes control within the previous 6 months; *12*) insulin pump therapy in the 2 months before screening or previous participation in any inhaled insulin trial; *13*) insulin requirement >150 units/day; and *14*) pregnancy, lactation, or planned pregnancy.

The study was conducted in accordance with the principles of the Declaration of Helsinki, and the protocol was approved by independent local institutional review boards.

Study design
This was an open-label, 24-week, parallel-group, multicenter study. After a 4-week run-in period, 335 patients were randomly assigned to receive premeal inhaled insulin plus bedtime subcutaneous Ultralente insulin or to continue the regimen received during the run-in period. This consisted of a conventional regimen: NPH and regular insulin before breakfast, regular insulin before dinner, and the second NPH insulin injection either before dinner or at bedtime.

After randomization, the subjects were seen weekly for the first 4 weeks and subsequently monthly throughout the treatment period. They met with a registered dietitian once during the run-in period and at week 12 to review a standardized American Diabetes Association meal plan. The importance of a meal plan was reinforced throughout the study, and the patients could consult the registered dietitian any time they needed. Thirty minutes of moderate exercise at least 3 days/week was also prescribed (8). The importance of the diet and exercise regimen was reinforced at each visit.

Treatment
Inhaled insulin was administered within 10 min before meals in conjunction with a single bedtime injection of Ultralente (Eli Lilly, Indianapolis, IN). Inhaled insulin was administered as a dry-powder formulation via an aerosol delivery system (Nektar Therapeutics, San Carlos, CA). Subjects were trained in the appropriate procedure for inhalation via verbal and videotaped instruction. Inhaled insulin was available in blister packs of 1- and 3-mg doses. Typically, one to three inhalations were administered for any given dose. Guidelines for initial premeal inhaled insulin doses were based on body weight and response to known doses of injected insulin (1 mg is equivalent to 2–3 units of subcutaneous insulin). The Ultralente dose was based on glycemic control, as well as the previous NPH insulin requirement.

Inhaled and subcutaneous insulin doses were adjusted based on the following glycemic goals, which were consistent with conventional treatment: fasting and premeal 80–140 mg/dl (4.4–7.8 mmol/l) and 100–160 mg/dl (5.6–8.9 mmol/l) before bedtime. The self-monitored blood glucose results were reviewed via telephone daily for the first 5 days and at each follow-up visit subsequently.

Assessments
The primary efficacy end point was the change in HbA$_{1c}$ from baseline to week 24. HbA$_{1c}$ was measured at screening and at weeks −1, 0, 6, 12, and 24. Secondary efficacy end points included changes in fasting plasma glucose (FPG) and 2-h postprandial glucose levels and percentage of subjects achieving HbA$_{1c}$ <7% at week 24. FPG was measured at weeks −4, −1, 0, 1, 12, and 24; postprandial glucose was measured at baseline and end of treatment after a 16-ounce Boost meal (Mead Johnson Nutritionals, Evansville, IN). A self-administered Diabetes Quality of Life and Treatment Satisfaction Questionnaire (Phase V Technologies, Wellesley Hills, MA) was completed at weeks −4, −1, 6, 12, 20, and 24. Hypoglycemia was defined as characteristic symptoms without glycemic measurement but promptly resolved with food intake or glucagon or intravenous glucose, or characteristic symptoms with blood glucose <60 mg/dl (3.3 mmol/l) or blood glucose <50 mg/dl (2.8 mmol/l) with or without symptoms. Hypoglycemia was defined as "severe" if subjects were unable to treat themselves, exhibited neurological symptoms, and had a measured blood glucose <50 mg/dl (2.8 mmol/l) or, if not measured, the clinical manifestations were reversed by oral carbohydrate, subcutaneous glucagon, or intravenous glucose.

Total, HDL, and LDL cholesterol and triglycerides were measured at weeks 0 and 24. A complete blood count with differential, urinalysis, and chemistries were performed at screening and week 24. A semiquantitative radioligand-binding assay was used to measure insulin antibodies at weeks 0 and 24.

A complete physical examination was conducted at screening, and a "brief" examination was conducted at weeks 0, 4, 8, 16, and 24 (weight, injection sites, pharynx, chest, heart rate, and blood pressure). Complete pulmonary function testing, using American Thoracic Society–certified methods, was performed at weeks −3 and 24. Measurement of forced vital capacity (FVC) and FEV$_1$ was also performed at week 12. Adverse events were recorded in all treated subjects and classified as mild, moderate, or severe.

Statistical analysis
This comparative trial was designed to test the "noninferiority" of the inhaled insulin regimen compared with the conventional insulin regimen. Analysis was performed for the per protocol (evaluable) population—a subset of the intention-to-treat population. The evaluable population included subjects who had no

2623

Table 1—*Characteristics at study entry of subjects receiving treatment with either inhaled or subcutaneous insulin*

	Inhaled insulin		Subcutaneous insulin	
	Male patients	Female patients	Male patients	Female patients
n	88	82	91	73
n aged <18 years	18	15	20	9
Age (years)	34.0 (12–63)	32.9 (11–63)	33.7 (11–61)	34.2 (12–64)
Weight (kg)	82.0 (49–131)	65.4 (35–91)	78.1 (38–110)	67.2 (40–93)
BMI (kg/m^2)	25.7 (17–36)	24.7 (18–34)	25.0 (18–32)	24.9 (18–33)
Duration of diabetes (years)	16.2 (1.0–41.0)		16.5 (1.0–49.0)	
n	164–169		159–162	
HbA$_{1c}$ (%)	8.33 (6.00–11.10)		8.30 (6.0–10.80)	
C-peptide (pmol/ml)	0.08 (0.07–0.26)		0.07 (0.07–0.23)	
Mean daily insulin dose (units)				
Short-acting insulin	21.00 (2.0–64.0)		21.28 (4.0–80.0)	
Long-acting/intermediate-acting insulin	35.37 (6.0–94.0)		34.48 (5.0–116.0)	

Data are means (range).

major violations of the inclusion/exclusion criteria, had received at least half the protocol-required duration of the treatments as assigned by the randomization scheme (12 of 24 weeks), and had one or more evaluable postbaseline HbA$_{1c}$ assessments (defined as having a treatment duration ≥75% of the elapsed time since the previous assessment). If the week 24 HbA$_{1c}$ value was not available, the last evaluable postbaseline assessment was carried forward (last observation carried forward). Changes from baseline HbA$_{1c}$ were assessed using an ANOVA model with terms for baseline HbA$_{1c}$, center, and treatment group. The 95% CI for the comparison of the inhaled insulin regimen and subcutaneous insulin regimen was derived from this model. Noninferiority of inhaled insulin to subcutaneous insulin was concluded if the upper limit of the 95% CI for the difference was <0.5% HbA$_{1c}$, as specified in the protocol. A similar analysis model was used for all other continuous variables.

The percentages of subjects reaching HbA$_{1c}$ <7% at week 24 were analyzed using logistic regression. The hypoglycemic event rate ratio was estimated using the survival analysis counting process approach for recurrent events, which only included a term for treatment. Multivariate ANOVA was used to test the overall null hypothesis of no treatment differences by analyzing the Quality of Life and Treatment Satisfaction scale changes from baseline to week 24. Safety analyses were performed for any subject who received at least one dose of study treatment.

Treatment group differences (inhaled − subcutaneous) in the change from baseline in FEV$_1$ and FVC were estimated at each assessment time point (weeks 12 and 24) using a repeated-measures ANCOVA model. The treatment group differences in change from baseline in DL$_{CO}$ and TLC at week 24 were estimated using an ANCOVA model. These models included terms for treatment and center, and covariates known to have a physiological relationship with pulmonary function, including baseline pulmonary function testing, age (years), baseline height (meters), and sex.

RESULTS — Of the 416 subjects screened, 335 were randomly assigned to receive treatment and one subject withdrew; therefore, 334 subjects received treatment (of whom 312 were evaluable for efficacy) and 303 completed treatment. Of the discontinuations in the inhaled insulin group, 6 were related to study treatment (3 adverse events—1 mild cough, 2 hypoglycemia—and 3 insufficient clinical response) and 12 were secondary to protocol violation or withdrawn consent or loss to follow-up. In the subcutaneous insulin group, 2 subjects discontinued because of insufficient clinical response and 11 for non–treatment-related reasons. The characteristics at study entry of the two study populations (90% white) are detailed in Table 1. The two treatment groups were well matched with the exception of a slight sex imbalance in the subcutaneous insulin group.

Efficacy
Baseline HbA$_{1c}$ values were 8.1 ± 1.0% in both groups. At week 24 (last observation carried forward), HbA$_{1c}$ was 7.9 ± 1.1% in the inhaled insulin group and 7.7 ± 0.9% in the subcutaneous insulin group with comparable mean decreases from baseline (adjusted treatment group difference: 0.16% [95% CI −0.01 to 0.32]) (Fig. 1*A*). The upper limit of the 95% CI was <0.5 (the prespecified noninferiority margin), indicating that the two treatment regimens are statistically comparable.

The percentage of subjects achieving HbA$_{1c}$ <7% at week 24 was comparable for the inhaled and subcutaneous insulin groups (15.9 and 15.5%, respectively) (adjusted odds ratio 0.92 [95% CI 0.40–2.10]). The inhaled and conventional insulin treatment regimen groups had similar baseline FPG values—194 mg/dl (10.8 mmol/l) and 203 mg/dl (11.3 mmol/l), respectively. At week 24, there was a greater reduction in the FPG in the inhaled insulin group (adjusted mean change from baseline −35 mg/dl [−1.9 mmol/l]) compared with the subcutaneous group (−10 mg/dl [−0.6 mmol/l]) (adjusted treatment group difference −25.17 mg/dl [95% CI −43.39 to −6.95]) (Fig. 1*B*). There was also a greater decrease in 2-h postprandial glucose in the inhaled group (adjusted mean change from baseline −30 mg/dl [−1.7 mmol/l]) compared with the subcutaneous group (1 mg/dl [0.06 mmol/l]) (adjusted treatment group difference −30.28 mg/dl [95% CI −54.6 to −6.0]).

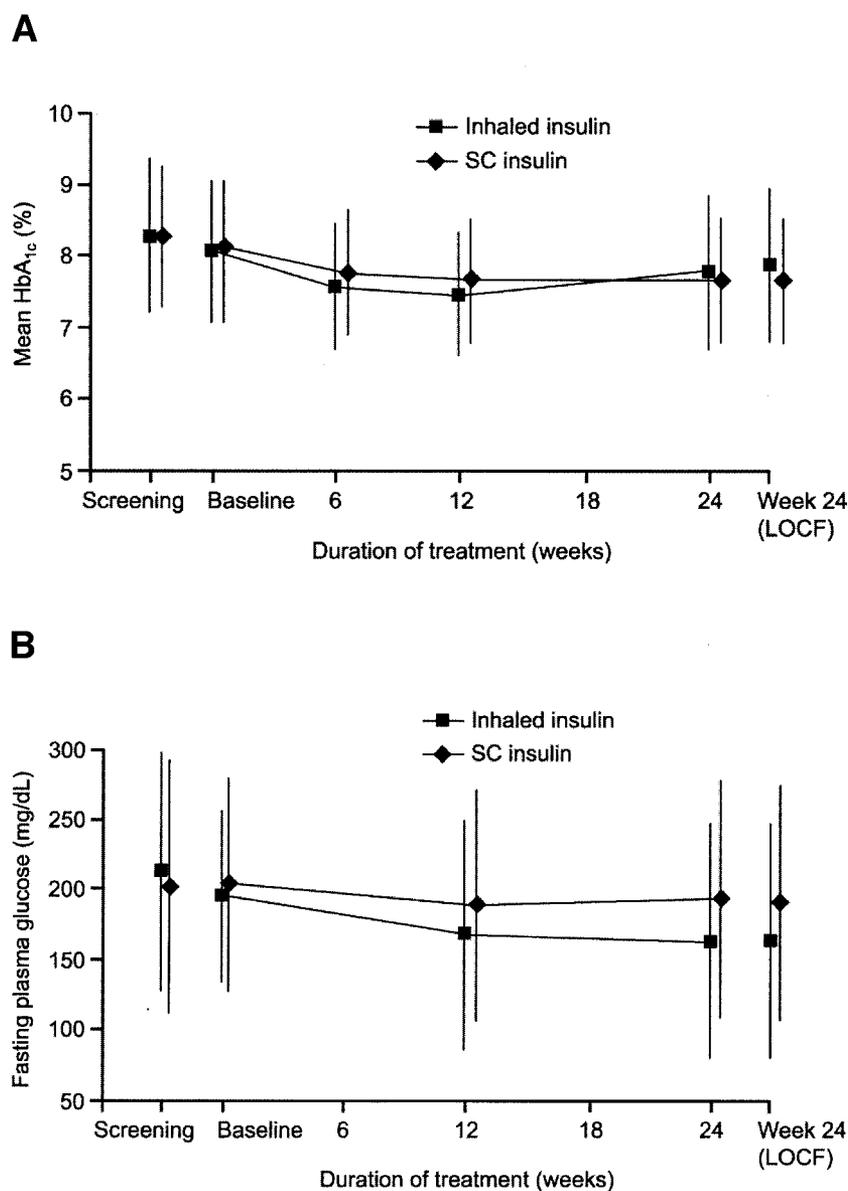The adjusted mean increase in body weight from baseline at week 24 was

A

B

Figure 1—A: *HbA$_{1c}$ levels in the inhaled and subcutaneous (SC) insulin groups, respectively, at screening (n = 156/153), baseline (n = 157/155), and weeks 6 (n = 153/147), 12 (n = 154/149), and 24 (n = 153/148). B: Mean change in FPG concentration in the inhaled and subcutaneous insulin groups, respectively, at screening (n = 154/152), baseline (n = 155/154), and weeks 12 (n = 148/149) and 24 (n = 147/144). LOCF, last observation carried forward.*

slightly less in the inhaled insulin group (0.9 kg) compared with that in the subcutaneous insulin group (1.5 kg), but this difference did not achieve statistical significance. The week 24 median changes from baseline in fasting lipid parameters in the inhaled and subcutaneous insulin groups, respectively, were as follows: total cholesterol, 1.0 and −5.0 mg/dl (0.03 and −0.13 mmol/l); HDL cholesterol, −1.5 and 1.0 mg/dl (−0.04 and 0.03 mmol/l); LDL cholesterol, 1.0 and −6.5 mg/dl (0.03 and −0.17 mmol/l); and triglycerides, 12.0 and 1.0 mg/dl (0.14 and 0.01 mmol/l).

At baseline, the daily short-acting and long-acting/intermediate-acting subcutaneous insulin doses were similar between the two groups (mean 18.4 and 39.3 units, respectively, in the inhaled group; 17.8 and 38.7 units in the subcutaneous group). The mean daily use of inhaled insulin changed only slightly during the study (from 12.4 to 14.2 mg). Mean insulin daily dose in the subcutaneous group remained relatively constant throughout the study

Safety and tolerability

The risk of overall hypoglycemia was lower in the inhaled insulin group compared with the subcutaneous insulin group (8.6 vs. 9.0 events/subject month; risk ratio 0.96 [95% CI 0.93–0.99]). In each group 155 patients reported a total of 7,536 (inhaled) and 7,806 events (sub-cutaneous insulin). There was no difference in severe events (5.5 vs. 4.7 events/100 subject-months, respectively; risk ratio 1.16 [95% CI 0.76–1.76]), with 29 (inhaled) and 21 (subcutaneous) patients experiencing a total of 48 and 41 events, respectively.

In both treatment groups, 99.4% of subjects experienced an adverse event during the study, with the most commonly reported being hypoglycemia. A greater number of subjects in the inhaled insulin group experienced cough (27 vs. 5%); however, these events were judged as mild to moderate and decreased in severity, incidence, and prevalence over the treatment period. With the exception of cough and overall hypoglycemia, the fre-

quency and nature of all-causality adverse events were comparable between treatment groups. All-causality adverse events were generally mild to moderate. Six adverse events in the inhaled insulin group and 11 in the subcutaneous group were reported as serious: 3 in each group were considered treatment-related and all involved hypoglycemia.

Pulmonary function test results are shown in Table 2. Mean changes in FVC, FEV_1, and TLC were comparable between the two groups. A greater mean decrease in DL_{CO} was observed for the inhaled insulin group without any clinical correlates.

Median insulin antibody percent binding was 29 and 3% in the inhaled insulin group and subcutaneous insulin group, respectively. This increase in antibody levels was not associated with any clinically significant findings (hypoglycemia or hyperglycemia, insulin dose, HbA_{1c}, pulmonary function testing, etc.). Vital signs, electrocardiogram, chest X-ray, and safety laboratory parameters were comparable in the two groups.

Patient-reported outcomes
The Overall Satisfaction Summary score improved significantly for the inhaled group ($P < 0.001$) and decreased significantly for the subcutaneous group ($P < 0.05$). All satisfaction subscales (advocacy, burden, convenience, efficacy, flexibility, general satisfaction, hassle, interference, pain, preference, side effects, and social) showed similar favorable effects associated with inhaled insulin treatment (all $P < 0.0001$). The overall quality-of-life scale and subscales of health perceptions, symptom interference, depression, positive affect, life satisfaction, psychological well-being, and cognitive function also showed more favorable improvements for the inhaled insulin group versus the subcutaneous insulin group ($P < 0.05$) (9).

CONCLUSIONS — This is the first large-scale study to compare the glycemic control provided by inhaled insulin plus a single injection of a long-acting subcutaneous insulin with that of a conventional subcutaneous insulin regimen in type 1 diabetes. Inhaled insulin provided glycemic control comparable with that of subcutaneous insulin, as assessed by the changes in HbA_{1c} from baseline to week 24 and the percentage of subjects achieving HbA_{1c} level <7% (10). The minimal

decrease in HbA_{1c} in both treatment groups is expected, given that the target glucose levels were set in keeping with conventional treatment. Nevertheless, inhaled insulin did lead to better control of FPG than subcutaneous insulin; however, the different baseline insulin used in the two groups could be a confounding factor.

These results are consistent with a previous small 12-week phase two study (6), and similar results have been obtained in subjects with type 2 diabetes (11). Data from an ongoing investigation also suggest that glycemic control is maintained during 24 months of inhaled insulin therapy (12). In the study by Skyler et al. (6), inhaled insulin had a comparable incidence of hypoglycemia to subcutaneous insulin. However, in the present study, the overall risk of a hypoglycemic event was lower in the inhaled insulin group. Cough of mild-to-moderate severity was observed with a greater frequency in the inhaled insulin group, although the incidence and prevalence of this decreased as the study progressed. Of notice is the fact that the subjects experiencing the cough did not have any symptom suggestive of respiratory distress at rest or during exercise. The nature and frequency of all other adverse events were comparable between the two treatment groups. FEV_1, FVC, and TLC were comparable over the treatment period in both treatment groups. Although a greater decrease in DL_{CO} was observed in the inhaled insulin group, this was not associated with any clinical or laboratory significant change. A possible mechanistic or methodologic basis for this difference and known variability of this measure may have played a role (13,14). In a long-term extension study of the Exubera Phase III program, changes in lung function initially observed remained small and nonprogressive. In a subset of patients in that study, controlled discontinuation of Exubera resulted in lung function gains similar in magnitude to the small decline observed in this study initially.

Insulin antibodies increased to higher levels in patients treated with inhaled insulin. In long-term extension studies, these levels tended to stabilize after the initial increase. There was no correlation of levels of antibody binding with parameters of metabolic control or safety, such as hypoglycemia, lung function, or insulin dose. Intraperitoneal insulin infusion is also known to increase insulin antibody

Table 2—Pulmonary function test results in subjects with a baseline and at least one postbaseline pulmonary function test measurement

Pulmonary function test parameter	Inhaled insulin			Subcutaneous insulin			Adjusted inhaled − SC difference in change from baseline at week 24	95% CI*
	Baseline	Week 12	Week 24	Baseline	Week 12	Week 24		
FEV_1 (l)	3.484 ± 0.806	3.432 ± 0.780	3.419 ± 0.767	3.433 ± 0.795	3.461 ± 0.809	3.435 ± 0.773	−0.031	−0.082 to 0.020
n	169	165	154	164	148	152		
FVC (l)	4.269 ± 1.033	4.235 ± 0.987	4.250 ± 0.967	4.234 ± 1.053	4.298 ± 1.052	4.271 ± 1.042	−0.018	−0.080 to 0.045
n	169	165	154	164	148	152		
TLC (l)	5.869 ± 1.413	—	5.908 ± 1.355	5.897 ± 1.409	—	6.073 ± 1.455	−0.087	−0.211 to 0.037
n	169	—	153	164	—	149		
DL_{CO} (ml · min^{-1} · mmHg^{-1})	28.435 ± 6.937	—	26.750 ± 6.746	28.136 ± 6.394	—	28.105 ± 6.850	−1.218	−1.950 to −0.485
n	167	—	153	163	—	149		

Data are means ± SD unless otherwise indicated. *For adjusted mean treatment group difference in change from baseline at week 24. SC, subcutaneous.

binding (15,16); whether this phenomenon is a general result of insulin exposure to large mucosal surfaces or formulation specific remains unclear. More recent data suggest that young age and insulin presensitization may play a role (17).

Similar to previous studies (6,11), a trend toward less weight gain was observed in the inhaled insulin group compared with the subcutaneous insulin group. This observation may lead to improved patient satisfaction if inhaled insulin were to be used in an intensive insulin regimen.

A questionnaire has recently been developed to allow assessment of patient satisfaction with alternative routes of insulin administration (18). Using this tool, previous investigators have reported greater overall satisfaction with inhaled insulin compared with subcutaneous insulin in patients with type 1 diabetes (6,7). This stemmed primarily from aspects relating to convenience and ease of use of inhaled insulin. Using a different questionnaire, the present study obtained similar findings: a higher acceptance among those administering insulin predominantly by inhalation compared with those on the conventional subcutaneous insulin injection regimen.

In conclusion, the results from this 24-week study suggest that inhaled insulin is effective and well tolerated in patients with type 1 diabetes. Combined with a single nighttime injection of long-acting insulin, preprandial inhaled insulin provided glycemic control comparable to that with a conventional subcutaneous insulin regimen with improved postprandial control. Thus, the use of inhaled insulin allowed the number of insulin injections to be minimized to just a single daily injection without compromising glycemic control, while adding increased flexibility of meal-related dosing. As a consequence, inhaled insulin was associated with improved patient satisfaction and quality of life—this may have important implications for therapeutic strategies aimed at increasing acceptance of intensive insulin regimens. Inhaled insulin may, therefore, be a valuable noninvasive component of therapy for patients with type 1 diabetes.

References
1. Diabetes Control and Complications Trial (DCCT) Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
2. Reichard P, Nilsson B-Y, Rosenqvist U: The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. *N Engl J Med* 329:304–309, 1993
3. Patton JS, Platz RM: Routes of delivery: case studies: pulmonary delivery of peptides and proteins for systemic action. *Adv Drug Deliv Rev* 8:179–196, 1992
4. Patton JS, Bukar J, Nagarajan S: Inhaled insulin. *Adv Drug Deliv Rev* 35:235–247, 1999
5. Heise T, Rave KM, Bott S, Sha S, Willavize SA, Carroll RS, Gruber S, Lee JD, Heinemann L: Time-action profile of an inhaled insulin preparation in comparison to insulin lispro and regular insulin (Abstract). *Diabetes* 49 (Suppl 1):A10, 2000
6. Skyler JS, Cefalu WT, Kourides IA, Landshulz WH, Balagtas CC, Cheng S-L, Gelfand RA, the Inhaled Insulin Phase II Study Group: Efficacy of inhaled insulin in type 1 diabetes mellitus: a randomised proof-of-concept study. *Lancet* 357:331–335, 2001
7. Gerber RA, Cappelleri J, Kourides IA, Gelfand RA: Treatment satisfaction with inhaled insulin in patients with type 1 diabetes. *Diabetes Care* 24:1556–1559, 2001
8. American Diabetes Association: Diabetes mellitus and exercise. *Diabetes Care* 21 (Suppl 1):40–44, 1998
9. Testa MA, Turner RR, Hayes JF, Simonson DC: Patient satisfaction and quality of life in type 1 diabetes: a randomized trial of injectable vs. inhaled insulin (Abstract) *Diabetes* 50 (Suppl. 2):A45, 2001
10. American Diabetes Association: Standards of medical care for patients with diabetes. *Diabetes Care* 26 (Suppl 1):33–50, 2003
11. Cefalu WT, Skyler JS, Kourides IA, Landschulz WH, Balagtas CC, Cheng S, Gelfand RA, the Inhaled Insulin Study Group: Inhaled human insulin treatment in patients with type 2 diabetes mellitus. *Ann Intern Med* 134:203–207, 2001a
12. Cefalu WT, Teeter JG, Lan S, Gelfand RA, Landschulz WH, the Inhaled Insulin Phase II Study Group: Sustained long-term efficacy and pulmonary safety of inhaled dry powder insulin. *Am J Respir Crit Care* 163:A163, 2001b
13. American Thoracic Society: Lung function testing: selection of reference values and interpretative strategies. *Am Rev Respir Dis* 144:1202–1218, 1991
14. American Association for Respiratory Care: American Association for Respiratory Care (AARC) Clinical Practice Guidelines: single-breath carbon monoxide diffusing capacity, 1999 update. *Respir Care* 44:539–546, 1999
15. Jeandidier N, Boivin S, Sapin R, Rosart-Ortega F, Uring-Lambert B, Reville P, Pinget M: Immunogenicity of intraperitoneal insulin infusion using programmable implantable devices. *Diabetologia* 38:577–584, 1995
16. Lassmann-Vague V, Belicar P, Raccah D, Vialettes B, Sodoyez JC, Vague P: Immunogenicity of long-term intraperitoneal insulin administration with implantable programmable pumps: metabolic consequences. *Diabetes Care* 18:498–503, 1995
17. Fineberg SE, Schatz D, Krasner A: Results of insulin antibody monitoring during phase II and III clinical studies of inhaled insulin (Exubera) in patients with type 1 or type 2 diabetes (Abstract). *Diabetologia* 45 (Suppl. 2):A17, 2002
18. Cappelleri JC, Gerber RA, Kourides IA, Gelfand RA: Development and factor analysis of a questionnaire to measure patient satisfaction with injected and inhaled insulin for type 1 diabetes. *Diabetes Care* 23:1799–1803, 2000